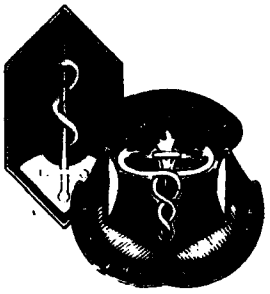

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Resuscitation of Conscious Pigs Following Hemorrhage: Comparative Efficacy of Small-Volume Resuscitation with Normal Saline, 7.5% NaCl, 6% Dextran 70, and 7.5% NaCl in 6% Dextran 70

C.E. Wade
J.P. Hannon
C.A. Bossone
M.M. Hunt
J.A. Loveday
R. Coppes
and
V.L. Gildengorin

DIVISION OF MILITARY TRAUMA RESEARCH

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Resuscitation of Conscious Pigs Following Hemorrhage: Comparative Efficacy of Small-Volume Resuscitation with Normal Saline, 7.5% NaCl, 6% Dextran 70, and 7.5% NaCl in 6% Dextran 70--Wade *et al.*

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The effect of small-volume resuscitation (4 ml/kg) with hypertonic saline/dextran (HSD) (7.5% NaCL in 6% Dextran, n=6), hypertonic saline (HS) (n=8), dextran (n=6), or normal saline (0.9% NaCl, n=8) was evaluated in chronically instrumented, splenectomized conscious swine bled 37.5 ml/kg over 60 min. Hemorrhage resulted in a reduction in cardiac index, stroke volume index, and mean arterial pressure. Survival with HSD (66%) was better than the other three treatments. The survival rate due to HS (25%) was greater than that due to normal saline (0%) but was not different than that of dextran (17%). HSD and HS expanded plasma volume by 33 and 29%, respectively. Administration of HSD or HS acutely improved
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cardiac index and stroke volume, and decreased heart rate. The increases in cardiac index and stroke volume were greater following resuscitation with HSD and the improvement persisted over 3 h. Mean arterial pressure was acutely increased after administration of HSD but returned to post-hemorrhage values within 30 min. Plasma Na^+ concentration and osmolality were increased to a similar extent with HSD and HS, while plasma K^+ levels were initially decreased, returning to control levels within 60 min. HSD appears to be a superior small-volume resuscitation solution compared to the other treatments with no detrimental effects noted in the present study of conscious swine.

ABSTRACT

The effect of small-volume resuscitation (4 ml/kg) with hypertonic saline/dextran (HSD) (7.5% NaCl in 6% Dextran, n=6), hypertonic saline (HS) (n=8), dextran (n=6), or normal saline (0.9% NaCl, n=8) was evaluated in chronically instrumented, splenectomized conscious swine bled 37.5 ml/kg over 60 min. Hemorrhage resulted in a reduction in cardiac index, stroke volume index, and mean arterial pressure. Survival with HSD (66%) was better than the other three treatments. The survival rate due to HS (25%) was greater than that due to normal saline (0%) but was not different than that of dextran (17%). HSD and HS expanded plasma volume by 33 and 29%, respectively. Administration of HSD or HS acutely improved cardiac index and stroke volume, and decreased heart rate. The increases in cardiac index and stroke volume were greater following resuscitation with HSD and the improvement persisted over 3 h. Mean arterial pressure was acutely increased after administration of HSD but returned to post-hemorrhage values within 30 min. Plasma Na+ concentration and osmolality were increased to a similar extent with HSD and HS, while plasma K+ levels were initially decreased, returning to control levels within 60 min. HSD appears to be a superior small-volume resuscitation solution compared to the other treatments with no detrimental effects noted in the present study of conscious swine.

INTRODUCTION

Hemorrhage is one of the major causes of death following trauma (1, 2), thus the rapid restitution of blood volume and therefore cardiovascular function are of paramount importance. Infusion of small volumes (4 ml/kg) of hypertonic and/or hyperoncotic solutions is effective in improving cardiovascular function following hemorrhage in a variety of species including humans (3-20). Hypertonic solutions cause an initial, transitory improvement (7-12). The addition of hyperoncotic colloids results in the persistence of the initial improvements elicited by hypertonic solutions (11-14). The effectiveness of these solutions has been attributed to their ability to mobilize fluids into the vascular space (7, 8, 11, 13). While a variety of studies have demonstrated the ability of these solutions to correct the detriment in cardiovascular function following hemorrhage, few studies have addressed the role of these changes in improving survival (5, 6, 12, 16). In the present study of conscious swine bled a fixed volume, we investigated post-hemorrhage survival over four hours following resuscitation with small volumes (4 ml/kg) of isotonic saline (NS) (0.9% NaCl), hypertonic saline (HS) (7.5% NaCl), hyperoncotic colloid (D) (6% Dextran 70), or a combination hypertonic/oncotic solution (HSD) (6% Dextran in 7.5% NaCl). Cardiovascular adjustments and fluid and electrolyte shifts were measured to assess their possible roles in survival.

METHODS

Twenty-eight immature Yorkshire pigs were used in this study. They were obtained from a commercial breeder and were housed in a common indoor laboratory holding facility for one to three weeks prior to experimentation. During this interval and subsequently the animals were fed a commercial chow (Purina Pig Chow, Ralston Purina Co., St. Louis, MO) and provided water ad libitum. For seven to ten days (three days before surgery and on days subsequent to recovery from surgery) the pigs were transported to the laboratory and familiarized with the surroundings, personnel, and handling procedures. The animals were trained to lie quietly in a modified Pavlov sling for one hour and to accept a snout respiratory mask.

After an overnight fast, each pig was transported to the operating room and administered a preanesthetic intramuscular injection of 0.8 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl, and 2.2 mg/kg xylazine. Halothane anesthesia was introduced by snout mask and maintained with an endotracheal catheter. A celiotomy was performed, the spleen was removed according to standard procedures (21), and a polyvinylidine sideport catheter (22) was implanted in the abdominal aorta for blood removal during hemorrhage. The free end of this catheter was tunneled under the skin and exited at the midlumbar region of the back. The animal was then repositioned, and catheters were implanted in the carotid and pulmonary arteries through a neck incision. Catheter placement was confirmed by noting the desired pressure wave form. The free ends of these catheters were tunneled under the skin and exited on the dorsal surface of the neck. These catheters were used for hemodynamic measurements and blood sampling. The exteriorized ends of all three catheters were fitted with stub adapters, capped with intermittent infusion plugs, and filled with heparinized saline (100 U/ml). The exit sites were protected with Velcro patches (5 cm x 10 cm) sutured to the skin; a hole (2 cm x 10 cm) was cut in the portion next to the skin to provide access. The animal was observed throughout post-operative recovery and then returned to its holding cage and provided food and water.

On the day of the experiment, following an overnight fast, each pig was transported to the laboratory, placed in the sling, and fitted with the snout respiratory mask, which was connected with a one-way Rudolph valve and 2.5 cm tubing to a Horizon System metabolic cart for the measurement of oxygen consumption. The carotid artery catheter was connected to a Statham P23db transducer by pressure-monitoring injection tubing and three-way stopcocks. Pressure was recorded with a Gould model 2400 recorder. After a period of 30 to 60 min, in which the animal rested quietly in the sling and exhibited stable values of oxygen consumption, the experiment was begun. Three sets of control measurements were then made at ten-minute intervals. Following

the last control measurement, a continuous fixed-volume hemorrhage was started from the abdominal aorta catheter. The hemorrhage schedule was designed to simulate an exponential rate of blood loss as it might occur in a severed artery in an extremity, the loss being stopped mechanically after one hour. Accordingly, successive 7.5-ml/kg increments were drawn continuously, with increments being completed after 9, 19, 31.5, 44, and 60 min. Total blood loss equaled 37.5 ml/kg. All measurements were repeated at the end of each increment of blood loss. Immediately after the completion of the hemorrhage, the animal was assigned to one of the following treatment groups:

1) Normal saline: 0.9% NaCl (n=8, 24.5±1.6 kg)

2) Dextran: 6% Dextran 70 in 0.9% NaCl (n=6, 21.7±1.0 kg; Macrodex, Pharmacia Laboratories, Piscataway NJ)

3) Hypertonic saline: 7.5% NaCl (n=8, 24.3±1.1 kg)

4) Hypertonic saline/dextran: 7.5% NaCl in 6% Dextran (n=6, 25.2±1.7 kg)

The treatment solution was injected as a bolus (4 ml/kg over 1 min) into the pulmonary artery. All measurements were then repeated at 5, 15, 30, 60, 120, 180, and 240 min after injection. At each time point, blood samples (30 ml arterial and 3 ml venous) were taken. The samples obtained during hemorrhage were included in the hemorrhage volume. Blood gases and acid-base values were obtained immediately after sample removal. The remaining samples were then partitioned into chilled test tubes and placed in ice water.

Blood gases were measured using an Instrumentation Laboratory system Model 1303 blood gas analyzer, and hemoglobin and oxygen content with an Instrumentation Laboratory cooximeter, Model 282. Plasma sodium and potassium concentrations were determined with an Instrumentation Laboratory flame photometer. Plasma osmolality was determined with an Advanced Instruments osmometer, Model 3D II, and oncotic pressure with a Wescor colloid osmometer, Model 4100. Plasma protein concentration was measured with an American Optical refractometer.

Cardiac index was calculated by the Fick equation. Heart rate was determined from the pulse pressure tracing. Stroke index, total peripheral resistance, and left ventricular work were calculated from standard formulas. The changes in plasma volume were calculated from changes in hematocrit.

To determine the significance of differences between groups, all parametric data were evaluated with two-factor analyses of variance adjusted for repeated measures. The time effect for the

hypertonic saline/dextran group was assessed using single-factor analyses of variance for repeated measures. Significant differences between the mean values were determined by Newman-Keuls tests. The survival data were analyzed using Breslow statistics for testing the equality of survival curves. Changes were considered significant when $P<0.05$. Values presented in the text are means $\pm$ SEM.

RESULTS

Survival

The combination of hypertonic saline/dextran increased survival significantly ($P<0.05$) compared to all other resuscitation solutions (Fig. 1). None of the animals survived beyond 40 min following treatment with isotonic saline. Administration of dextran did not significantly improve survival. Resuscitation with hypertonic saline increased ($P<0.05$) survival compared to isotonic saline, but was not different from dextran.

Of the six pigs entered into the hypertonic saline/dextran group, four survived the complete experiment. Two animals died, one at 70 min after treatment with hypertonic saline/dextran and another at 190 min. To compensate for the inter-animal variability resulting from the deaths of these two animals, two means were calculated for the times immediately preceding these deaths: one mean included and the other excluded the nonsurviving animals.

In the comparison of data between groups the values at the onset of hemorrhage, end of hemorrhage and at 5 min post treatment were used. These time points are used because the 5-min post-treatment value is the only time at which all groups were complete. For instance, after 5 min in the normal saline group, only five of the animals survived. The loss of animals thus makes comparisons between groups inappropriate beyond the 5 min time point.

RESPONSES TO HEMORRHAGE AND RESUSCITATION

There were no significant differences between groups in any of the measured variables prior to hemorrhage. The responses of the measured variables to hemorrhage were not significantly different ($P>0.05$) between the groups of animals (Tables I and II).

Cardiac index was reduced in all groups during hemorrhage (Table I). Five minutes following resuscitation, cardiac index was increased in the animals treated with the hypertonic saline/dextran and hypertonic saline solutions. However, there was a significant between-group difference in the improvement; cardiac index increased 46 ± 6 ml/min/kg with hypertonic saline and

104±9 ml/min/kg with hypertonic saline/dextran. At 5 min after treatment with hypertonic saline/dextran, the cardiac index was equivalent to control values. Thereafter, cardiac index fell but was persistently greater than the level recorded at the end hemorrhage (Fig. 2).

Mean arterial pressure decreased during hemorrhage (Table I). Administration of isotonic saline, dextran, or hypertonic saline failed to increase mean arterial blood pressure. Mean arterial pressure was acutely increased after resuscitation with hypertonic saline/dextran but did not attain control values. Following the initial increase immediately after treatment, mean arterial pressure fell to a level that was not different than that at the end of hemorrhage.

Heart rate was increased and stroke index decreased during hemorrhage (Table I). Although the magnitude of the increase in heart rate during hemorrhage was variable between groups, a significant difference was not noted. Heart rate was reduced by hypertonic saline and the combination solution (Table I). The decrease in heart rate was accompanied by an increase in stroke index (Fig. 2). The increase in stroke index following treatment was greater with hypertonic saline/dextran than with hypertonic saline alone. The changes in heart rate and stroke index following administration of hypertonic saline/dextran did not persist throughout the recovery period. Heart rate increased during the recovery period following hypertonic saline/dextran and attained values similar to those recorded at the end of hemorrhage. Stroke index also fell over the recovery period after the combination treatment but was maintained at values greater than those at the end of hemorrhage.

Total peripheral resistance was unchanged during hemorrhage (Table I). After the administration of either hypertonic saline or hypertonic saline/dextran, total peripheral resistance was acutely reduced. During the recovery period following hypertonic saline/dextran, total peripheral resistance increased, returning to prehemorrhage control levels (Fig. 2). Left ventricular work was elevated following the hypertonic saline/dextran, but fell over the period of recovery (Fig. 2).

Plasma sodium concentrations were not altered during hemorrhage or following treatment with isotonic saline or dextran (Table II); however, both hypertonic solutions significantly increased plasma sodium levels, 11±1 mEq/l with hypertonic saline and 8±1 mEq/l with hypertonic saline/dextran. The increase in plasma sodium following hypertonic saline/dextran continued through the recovery period (Fig. 3). Plasma potassium tended to rise during hemorrhage but was not significantly altered. However, within 5 min after treatment with isotonic saline a significant increase was noted. Plasma potassium was reduced

equally, 1.7 mEq/l, with both hypertonic solutions. Plasma potassium, while initially decreased after both hypertonic saline and hypertonic saline/dextran, returned to control levels by 60 min (Fig. 3).

Plasma osmolality was increased during hemorrhage and was further increased by the hypertonic saline and the hypertonic saline/dextran treatments, an effect that persisted throughout the recovery period. In all four groups plasma oncotic pressure was progressively decreased during hemorrhage, the decrements ranging from 4.0 to 2.5 mmHg. Treatment with dextran returned plasma oncotic pressure to control levels, whereas hypertonic saline produced a further reduction of 2.3±0.6 mmHg. Five minutes following treatment with hypertonic saline/dextran, oncotic pressure was not immediately changed. However, over the recovery period it rose, increasing significantly compared to the level at the end of hemorrhage.

Plasma protein concentrations were decreased over the hemorrhage (Table II). Treatment with either hypertonic saline solution resulted in a further reduction (0.7±0.2 g/dl with hypertonic saline and 0.6±0.1 g/dl with hypertonic saline/dextran). Over the recovery period following hypertonic saline/dextran administration, plasma protein levels were significantly increased.

Hemorrhage progressively decreased hematocrit levels and hemoglobin concentrations (Table II). After all treatments except isotonic saline, hematocrit and hemoglobin levels were further decreased. During the recovery period hypertonic saline/dextran produced no additional changes in hematocrit (Fig. 3) or hemoglobin. The ratio of hemoglobin to hematocrit was not significantly altered by hypertonic saline/dextran, being 0.304±.003 before hemorrhage, 0.296±0.014 at the end of hemorrhage, and 0.298±0.012 at 5 min after treatment. The calculated acute changes in plasma volume 5 min after treatment were 6.6±2.7% with isotonic saline, 21.7±2.5% after dextran, 29.5±2.6% following hypertonic saline, and 32.6±2.4% with hypertonic saline/dextran. The increase in plasma volume following hypertonic saline/dextran persisted throughout the four hours of recovery.

DISCUSSION

The improvement of survival after resuscitation with hypertonic saline/dextran is consistent with earlier work reported by Maningas et al (12). However, they did not observe improved survival with hypertonic saline alone, as others have (5, 6, 16), and did not show a significantly greater effect with the combination solution compared to dextran alone. In our study, hypertonic saline also improved survival but to a significantly lesser extent than hypertonic saline/dextran.

Dextran alone failed to increase survival. Although Maningas et al (12) also employed conscious swine, differences in survival may be attributed to a variety of factors: animal surgical preparation, bleeding volume and duration, and resuscitation volume. They used a different hemorrhage procedure (46 ml/kg over 15 min compared to our 37.5 ml/kg over 60 min). Their animals were neither splenectomized nor restrained in a Pavlov sling as in our study, and they used a greater volume of resuscitation solution (11.5 ml/kg compared to our 4 ml/kg). These procedural disparities may explain the differences in survival recorded in the two studies. Nevertheless, both investigations show that resuscitation with small volumes of hypertonic saline/dextran significantly improves the survival of animals subjected to severe hemorrhagic hypotension as compared to equal volume normal saline resuscitation.

In comparison to earlier experimental work with hypertonic solutions, our study and that of Maningas et al (12) are unique; both employed a fixed-volume, normally lethal hemorrhage model. Other investigators (5-11, 13, 15-17) have used the Wiggers (fixed-pressure) model, which does not allow complete expression of the compensatory changes that normally occur during the period of hemorrhagic hypotension (23). Although the Wiggers model provides reproducible hemodynamic changes during and following hemorrhage, it may compromise the effectiveness of the resuscitation fluids being evaluated. The Wiggers procedure, for example, can lead to irreversible deterioration of the peripheral circulation (23), an effect that has little relevance to the hemorrhagic hypotension seen in trauma victims (24). Furthermore, this deterioration of peripheral circulation could readily alter the hemodynamic responses to resuscitation. To further complicate the issue, anesthesia is commonly used in shock studies based on a fixed-pressure model. These differences in the hemorrhage models must be considered when comparing our findings to those of others.

What functional changes could account for improved survival following resuscitation with hypertonic/dextran compared to hypertonic saline alone? One effect could be the restoration of cardiac function. Hypertonic saline/dextran produced a significantly greater increase in cardiac output than hypertonic saline alone; at the 5-minute point after resuscitation the former was elevated to 114% of control levels, the latter to 74%. This early response difference has not been observed in other investigations. Smith et al (11) and Kramer et al (13) have thus shown in sheep subjected to a moderate, nonlethal, fixed-pressure hemorrhage that administration of hypertonic saline/dextran or hypertonic saline alone at 4 ml/kg produced increases in cardiac index equivalent to control levels or above. Furthermore, this restoration of cardiac index persisted for over 120 min after treatment. Maningas (14) noted a similar response to hypertonic

saline/dextran in swine subjected to a much more severe, fixed-volume hemorrhage. The results of these investigations are in contrast to our study, in which cardiac index was transiently returned to the basal level but subsequently decreased to 77% of control at one hour after treatment. The value at 60 min, although still greater than that observed at the end of hemorrhage, suggests that factors other than prolonged improved cardiac output may be contributing to survival. The response difference in cardiac index seen in our study (compared to Smith et al (11) and Kramer et al (13) may be due to hemorrhage severity and (compared to Maningas (14)) to the smaller volume of resuscitation solution used.

In our study, heart rate was reduced after treatment with both hypertonic solutions. Therefore, tachycardia did not contribute to the improvement in cardiac index. Investigators studying the combination solution reported no change in heart rate (11-13), or, when evaluating hypertonic saline alone, they reported an increase, decrease or no change in heart rate (5, 8, 11, 12, 16). A decrease was observed in our study. These response differences may be species-related or model dependent. The studies of Smith et al (11) and Velasco and co-workers (5) were conducted with sheep and dogs, respectively. Although Maningas et al (12) observed an increase in heart rate during hemorrhage in swine, they did not record a change in heart rate after treatment with hypertonic saline or hypertonic saline/dextran. In view of these response differences it would seem reasonable to conclude that changes in heart rate did not contribute to improved survival following resuscitation with either hypertonic saline or hypertonic saline/dextran.

An augmented stroke index was the primary contributor to the increase in cardiac index observed here as well as in earlier studies of hypertonic saline/dextran (11, 13, 14) and hypertonic saline alone (5, 11). An elevated stroke volume, therefore, could be a critical contributor to improved survival as heart rate was decreased. The augmentation seen here and in other studies was due, presumably, to improved venous return and thus cardiac filling, effects that could be mediated by one or more of the following factors: a direct or indirect vasodilatory action of hypertonic sodium; fluid mobilization into the vascular space with resultant recovery of vascular volume, or a reduction in blood viscosity.

It is now well established that hypertonic saline causes prompt vasodilation when infused into local vascular beds. This effect has been recorded in isolated extremities, as well as in the coronary, lung, and renal preparations (25-31). In addition to these direct vascular actions, Lopes et al (6) and Younes et al (10) have presented evidence of an indirect, vagally-mediated effect of hypertonic saline. Activation of this neural pathway via undefined receptors in the lung produced increases in mean

arterial pressure and cardiac output. Most observers also report a decrease in peripheral resistance following resuscitation with hypertonic saline or hypertonic saline dextran (3, 5, 8, 11, 13), but one cannot readily discern the extent to which this response is attributable to the direct or indirect (neural) effects of the resuscitation solutions on the tone of peripheral vasculature. Confusing the issue are the increases in cardiac output and the impact of these increases on the calculated values for peripheral resistance, which, after all, represents the ratio of mean arterial pressure to cardiac index, and a change in either of these variables produces a change in calculated resistance. Similarly, hemorrhage produces marked increases in the plasma levels of vasoactive hormones, particularly epinephrine and norepinephrine, and little is known about the peripheral vascular impact of resuscitation-induced reductions in the concentrations of these hormones. In any event, neither our data nor the data of others provide any evidence that the peripheral vascular actions of hypertonic saline/dextran are any different from those of hypertonic saline alone.

Along similar lines, it is well known that a reduction in venous capacity is one of the normal compensatory responses to hemorrhagic hypotension and that this effect is attributable to an increase in venous tone (32, 33). A reduction in venous capacity translates into an increase in effective blood volume, i.e., a smaller anatomic blood volume can support the nutrient flow to body tissues. Potentially, resuscitation solutions could enhance this response. Evidence supporting such enhancement was recently reported by Lopes et al (17) and Rocha e Silva et al (16) who showed that mean circulatory pressure was increased significantly following intravenous administration of hypertonic saline to hypotensive dogs. This increase was attributed to venoconstriction and appeared to be neurally mediated over afferent pathways in the vagus. Differences in venous capacity due to an effect of hypertonic saline do not appear to be responsible for improved survival of pigs resuscitated with hypertonic saline/dextran since they received the same amount of NaCl as pigs resuscitated with hypertonic saline alone which did not survive as well.

Improved venous return could be due in part to the increase in plasma volume that occurs with treatment. Accordingly, administration of hypertonic saline causes an osmotically induced redistribution of water from the intracellular to the interstitial space and thus to the vascular compartment. The transient nature of this fluid transfer has been described previously (5, 8, 9, 11, 15). Velasco et al (5) reported that the administration of hypertonic saline following hemorrhage produced an expansion of blood volume that lasted less than 30 min. Nakayama et al (8, 9) found plasma volume to be expanded

and intracellular water content to be reduced within minutes of the administration of hypertonic saline with a trend to return to post-hemorrhage distributions after 60 min. The addition of dextran, because of its oncotic properties, promotes retention of this water in the vasculature. This effect of dextran was reported by Smith et al (11) who showed clearly that dextran maintained the expansion of plasma volume initially induced by hypertonic saline. The ultimate effect, an increased blood volume, presumably improves venous return, hence cardiac output. Reported increases in central venous pressure following resuscitation with hypertonic saline support this conclusion (8, 13). The initial expansion of vascular volume, however, cannot account fully for the differential effects of hypertonic saline and hypertonic saline/dextran seen in our study. As judged from hematocrit changes following resuscitation, the increase in volume was similar after administration of both hypertonic saline/dextran and hypertonic saline alone, yet the increase in cardiac index was significantly greater in the former than in the latter. The presence of dextran, however, could have enhanced survival because the cardiac output of the hypertonic saline/dextran pigs did not revert to post-hemorrhage levels during the course of recovery as it did in the pigs treated with hypertonic saline. This beneficial effect appeared attributable to the maintenance of an improved vascular volume by the oncotic action of dextran; subsequent to an initial resuscitation decrement, hematocrit values gradually rise in pigs that receive hypertonic saline alone (unpublished data).

Reduced blood viscosity can enhance venous return by increasing blood fluidity which in turn reduces flow impedance in the microvasculature (32-34). Dextran has such an effect in vivo; hence its presence could potentially account for the greater improvement in cardiac output seen in pigs resuscitated with hypertonic saline/dextran. The effect of dextran, however, is largely, if not entirely, due to hemodilution (35), and in our study the degree of hemodilution (as judged by hematocrit changes) was essentially the same in pigs resuscitated with dextran, hypertonic saline, and hypertonic saline/dextran. Consequently, viscosity differences did not contribute to the more pronounced cardiac output response seen in animals resuscitated with hypertonic saline/dextran. Therefore, enhanced survival of these animals was probably due to the oncotic properties of dextran. In this regard, dextran-induced retention of water translocated from intracellular to intravascular space would seem to be of prime importance. Failure to retain this water could lead to either interstitial edema with a resultant impairment of capillary-to-cell O_2 diffusion (35) or, potentially, interstitial pressures that exceeded the critical closing pressure, hence, an increase in the rate of transcapillary water loss.

In comparing the acute increase in cardiac index following the administration of the hypertonic saline/dextran to that at one hour after treatment, two components contributing to the increase may be identified: an increase in blood volume and reduction in the neuromodulation of vascular tone (6, 10, 13). The initial response may be the product of both the increase in blood volume and changing neuromodulation of vasculature tone. At one hour cardiac index was increased above the value at the end of hemorrhage by 39 ml/kg/min compared to 104 ml/kg/min at 5 min after treatment. As vascular volume was not changed over the hour it could be assumed that 38% of the acute increase in cardiac index is the result of the increase in volume and the other 62% is caused by other factors. Of importance in this assumption is that at one hour total peripheral resistance was at normal levels, while immediately after treatment it was pronouncedly reduced, suggesting a transitory effect on vascular tone which could be the product of neural modulation.

The improvement in venous return, and thus cardiac index, after administration of the hypertonic saline/dextran solution may therefore occur in the following manner: vascular volume increases, venous capacity is reduced, and viscosity is decreased. These changes do not result in adequate improvement in venous return to sustain cardiac index and thus life when hypertonic saline or dextran are administered alone. Nevertheless, the combination of these solutions in the form of hypertonic saline/dextran does. The effects elicited by hypertonic saline and dextran alone could be additive, resulting in the effective combination solution. Accordingly, as the increase in cardiac index, and presumably venous return, was 74 ± 16 % with hypertonic saline alone and with dextran 33 ± 17%, the combination of the components contributing to these increases could result in the observed 118 ± 22% increase with hypertonic saline/dextran.

In the use of hypertonic saline/dextran as a resuscitation solution, concern has been raised about potential dysfunctions attributable to hypernatremia and hypokalemia (19). Concern about hypernatremia arises in part from the assumption that the injected sodium loads will remain primarily in the vascular compartment. The administration of the combination solution in our study did not result in hypernatremia or hypokalemia of clinical significance, nor have other investigators reported any overt signs. The absence of any adverse effects is not too surprising. Thus, five minutes after the administration of hypertonic saline/dextran, plasma sodium concentration was increased by only 8 mEq/l or 6%. Holcroft et al (20) reported a similar increase in plasma sodium in patients who received the combination solution, namely 11 mEq/l. In our study hypernatremia persisted throughout the four-hour recovery subsequent to resuscitation. The modest increase in plasma

sodium seen in our study as well as by others (11-13, 20) appears to be due to rapid fluid mobilization from the intracellular space and a high capillary permeability to sodium which would facilitate its transfer to the interstitial space. If it is assumed that 62% of body water is in cells, the amount moved to the extravascular space by the administration of the combination solution would represent only a 5% decrease in intracellular water. The movement of this water into the extracellular space could readily account for the hypokalemia seen in the present study and reported also by others (4, 11-13, 20). Plasma potassium levels, furthermore, were only acutely reduced following resuscitation with hypertonic saline/dextran and reverted to control concentration by 60 min of recovery. The presence of hypernatremia and hypokalemia, therefore, does not appear to be a significant problem following the administration of hypertonic saline/dextran, especially in light of its resuscitative capabilities.

In summary, small-volume resuscitation with 4 ml/kg of a hypertonic saline/dextran solution improves survival following hemorrhagic hypovolemia in conscious immature swine by increasing cardiac output, in response to an elevation of stroke volume index. The increase in stroke volume index is facilitated by a variety of factors (expansion of plasma volume, vasodilation of the peripheral vasculature, reduced venous capacity, and reduced blood viscosity and flow impedance in the microvasculature). Detrimental effects of hypertonic saline/dextran resuscitation were negligible in our study of conscious swine subjected to a normally lethal fixed-volume hemorrhage.

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TABLE I. Hemodynamic Changes from Control (C), after Hemorrhage (H), and 5 Min after Small Volume Resuscitation (T).

	NS[a]	D[b]	HS[c]	HSD[d]
Cardiac Index (ml/kg/min)				
C	150±8	132±9	167±8	177±16
H	91±13*	81±13*	77±12*	98±14*
T	104±13*	107±20*	123±7*+	202±19+
Mean Arterial Pressure (mmHg)				
C	105±6	99±4	103±3	107±3
H	55±3*	62±7*	54±4*	52±8*
T	56±5*	62±3*	65±3*	84±4*+
Heart Rate (beats/min)				
C	113±3	110±5	115±4	116±4
H	204±20*	191±15*	185±15*	170±19*
T	214±17*	187±15*	158±12*+	148±13*+
Stroke Index (ml/kg/min)				
C	1.23±0.05	1.22±0.10	1.47±0.13	1.52±0.14
H	0.57±0.08*	0.44±0.07*	0.42±0.06*	0.61±0.10*
T	0.59±0.07*	0.60±0.13*	0.83±0.09*+	1.40±0.16+
Total Peripheral Resistance (mmHg/kg/min/ml)				
C	0.72±0.04	0.77±0.08	0.62±0.03	0.63±0.07
H	0.64±0.05	0.88±0.17	0.76±0.10	0.53±0.05
T	0.61±0.07	0.71±0.14	0.53±0.03+	0.43±0.03+

TABLE I (cont.)

	NS[a]	D[b]	HS[c]	HSD[d]
Left Ventricular Work (dynes/cm^2)				
C	220±31	176±10	233±13	257±25
H	72±12*	68±14*	57±11*	76±22*
T	87±17*	91±18*	109±9+	236±32+

[a] NS=normal saline ("isotonic" in text)
[b] D=dextran
[c] HS=hypertonic saline
[d] HSD=hypertonic saline/dextran
* significantly different from C ($P<0.05$)
+ significantly different from H ($P<0.05$)

TABLE II. Blood and Plasma Constituents from Control (C), after Hemorrhage (H), and 5 Min after Treatment with Small Volume Resuscitation (T).

	NS[a]	D[b]	HS[c]	HSD[d]
Na^+(mEq/l)				
C	136±2	137±2	140±2	138±2
H	139±2	133±3	138±1	135±2
T	139±2	135±3	149±1*+	143±3*+
K^+ (mEq/l)				
C	4.2±0.1	4.1±0.1	4.2±0.2	4.0±0.1
H	5.3±0.2	4.8±0.5	5.0±0.3	4.7±0.3
T	5.7±0.4*	4.4±0.8	3.6±0.2+	3.3±0.3*+
Osmolality (mOsm/kg)				
C	277±1	280±1	281±1	279±1
H	296±3*	299±5*	294±3*	289±1*
T	300±3*	301±6*	310±2*+	307±2+*
Oncotic Pressure (mmHg)				
C	18.5±0.5	17.2±1.9	16.6±0.3	15.7±0.8
H	14.5±0.9*	14.7±1.3*	13.2±0.6*	12.5±0.8*
T	13.8±0.9*	16.9±1.6	10.9±0.3*+	12.4±0.7*
Protein (g/dl)				
C	6.7±0.1	5.9±0.1	6.0±0.1	5.6±0.2
H	6.0±0.2*	5.4±0.2	5.2±0.2*	4.9±0.2*
T	5.8±0.2*	5.2±0.2*	4.5±0.1*+	4.3±0.1*+

TABLE II (cont)

	NS[a]	D[b]	HS[c]	HSD[d]
Hematocrit (%)				
C	33±2	33±1	33±1	31±1
H	26±2*	25±1*	24±1*	22±1*
T	25±2*	22±1*+	20±1*+	18±1*+
Hemoglobin				
C	9.9±0.7	10.3±0.3	9.9±0.4	9.3±0.5
H	7.5±0.5*	7.5±0.4*	8.0±0.3*	6.7±0.4*
T	7.0±0.4*	6.4±0.3*+	6.6±0.3*+	5.3±0.3*+

[a] NS=normal saline ("isotonic" in text)
[b] D=dextran
[c] HS=hypertonic saline
[d] HSD=hypertonic saline/dextran
* significantly different from C ($P<0.05$)
+ significantly different from H ($P<0.05$)

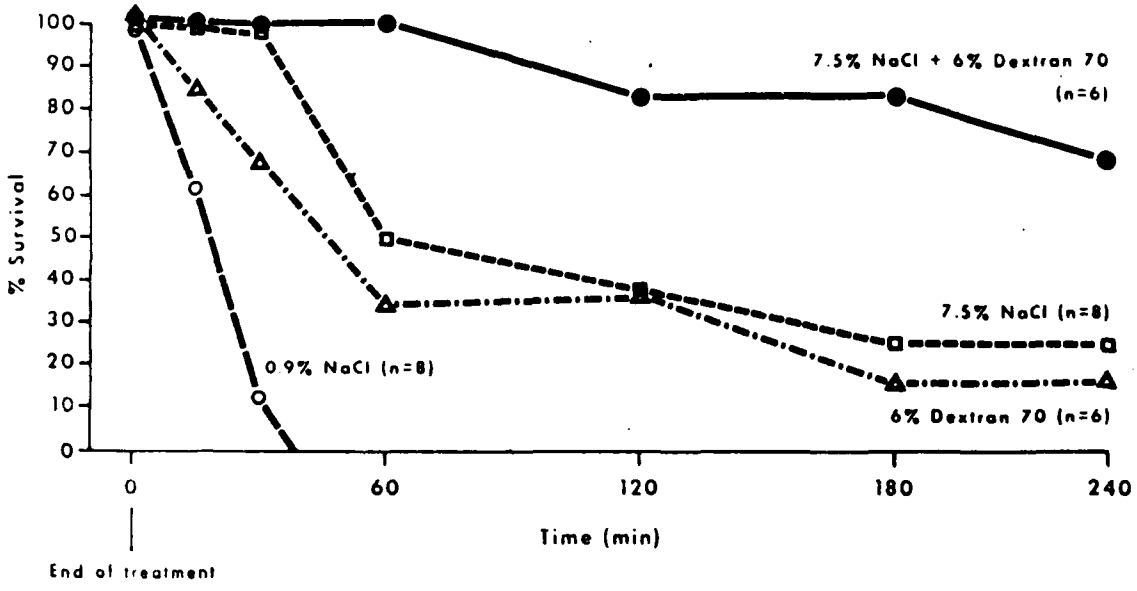

Fig. 1: Percent survival following small volume (4 ml/kg) resuscitation for hemorrhagic hypotension with normal saline (n=8), dextran (n=6), hypertonic saline (7.5% NaCl; n=8), and hypertonic saline/dextran (7.5% NaCl in 6% Dextran; n=6). Hypertonic saline/dextran improved survival compared to all other groups, while hypertonic saline alone was greater than control.

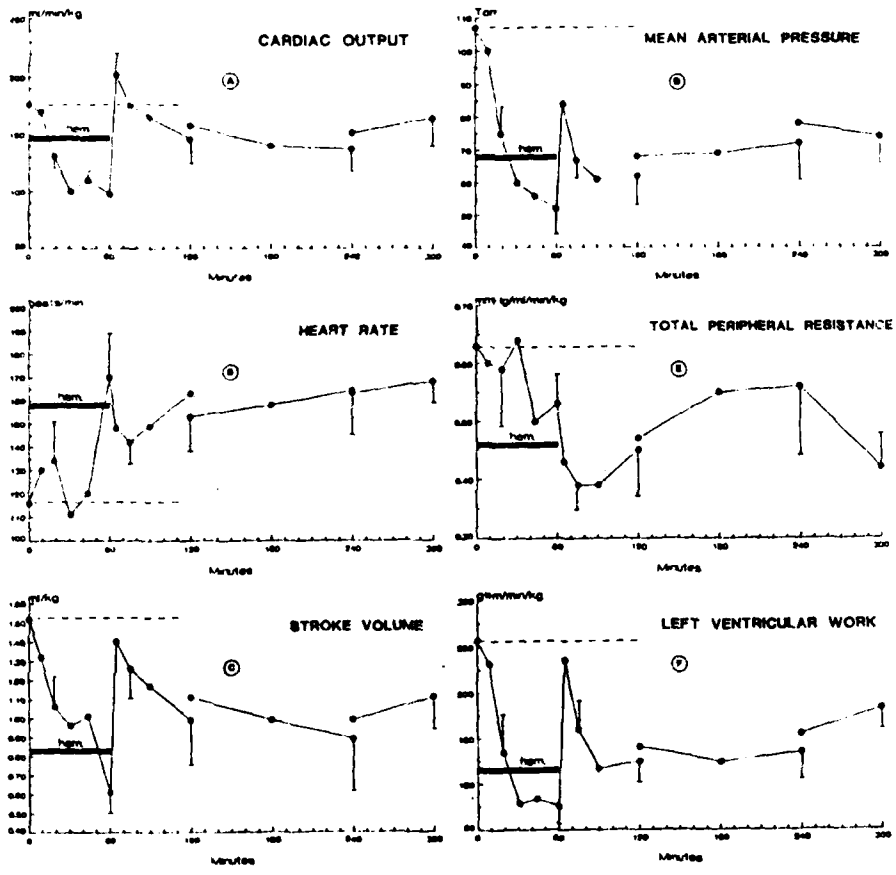

Fig. 2: Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl in 6% Dextran on cardiovascular function. Resuscitation was provided (over 1 min) after hemorrhage. Breaks in the plots indicate time points at which mean and SEM values were calculated to include as well as exclude animals that died shortly thereafter. The solid bar depicts hemorrhage interval and the dashed line control levels for each variable.

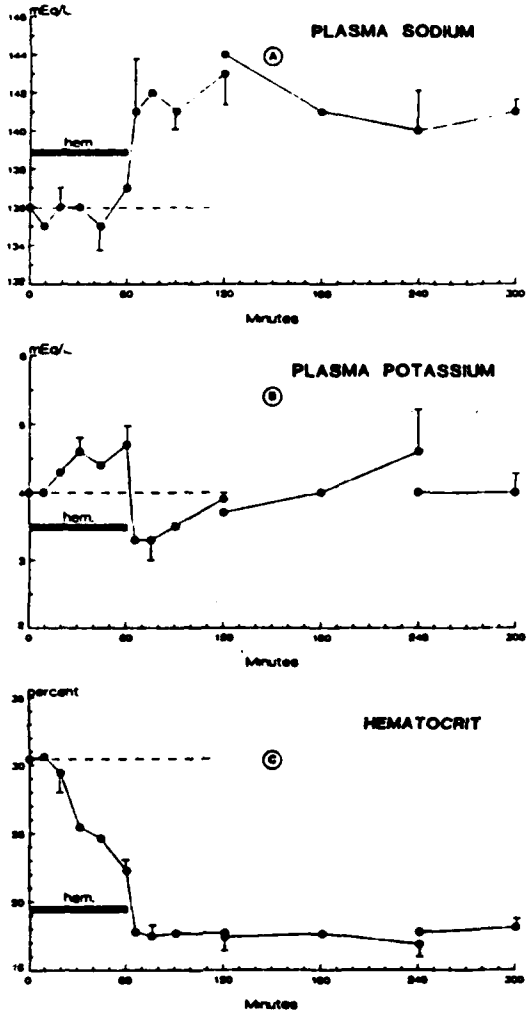

Fig. 3: Effects of progressive fixed volume hemorrhage followed by resuscitation with hypertonic saline/dextran on plasma sodium and potassium concentrations and hematocrit levels. See Fig. 2 for details.

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